Electronic Supplementary Material (ESI) for RSC Advances.

SUPPORTING INFORMATION

First ligand-free, microwaves-assisted, Heck cross-coupling reaction in sole water on nucleoside - Application to the synthesis of antiviral BVDU

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Experimental

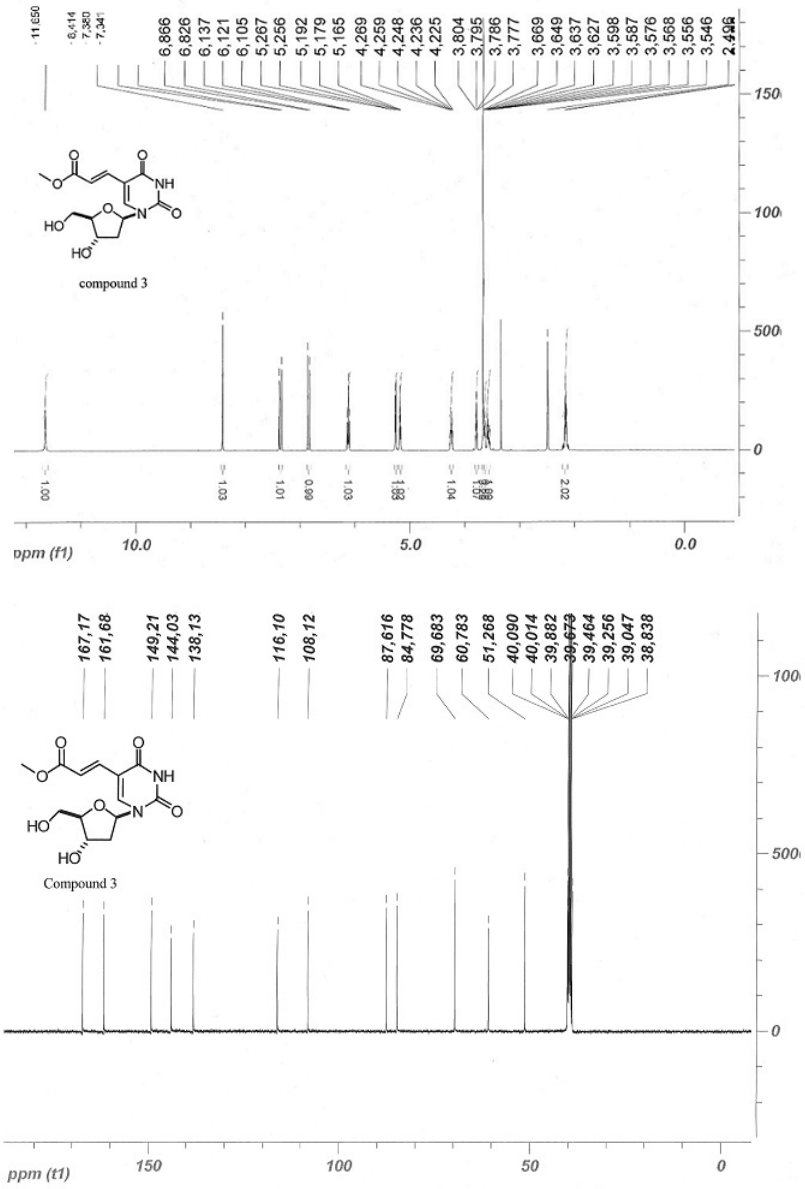
Materials and methods

All products were purchased either to Fisher Scientific or Sigma Aldrich depending on their availability. All Solvents were purchased to Fisher Scientific. All reactions were monitored by HPLC. The column used is a GRACE Prevail C18. The detectors used are SPD-M20A photo diode array detector (Shimadzu), LCMS-2020 mass spectrometer (Shimadzu) and ELSD-LTII (Shimadzu). The mobile phase is a mixture of water and MeOH (50:50). Mass spectrometry analyses were performed on a Shimadzu LCMS-2020 mass spectrometer equipped with an electrospray source (ESCI). High-resolution electrospray mass spectra (HRMSESI) in the positive ion mode were obtained with a Waters-Micromass Q-TOF Ultima Global hybrid quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (Zspray) ion source (Waters-Micromass, Manchester, UK). 1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker UltraShield 400MHz/54mm Ultra long hold. Chemical shifts (δ) are quoted in ppm and are referenced to TMS as an internal standard. Coupling constants (J) are quoted in Hz. Melting points are recorded on a Stuart SMP 10 and are uncorrected.

General procedure for the totally aqueous ligand-free Heck cross couplings.

5-iodo-2′-deoxy-uridine (100 mg, 0.28 mmol, 1 equiv.), triethylamine (78 µL, 0.56 mmol, 2 equiv.) acrylate (or acrylate derivative) (1.12 mmol, 4 equiv.) and $Pd(OAc)_2$ (6.4 mg, 10 mol%) were placed in a 10 mL microwave vial. Freshly degazed water (18.2 MΩ, 2mL) was added. The mixture was stirred under microwave irradiation (AntonPaar Monowave 300) at 80°C for 30 minutes. The crude mixture was purified by flash-chromatography on C18 silica (H_2O:MeOH 95:5 to 5:95). The fractions were combined and methanol was removed under reduce pressure. The remaining solution was frozen with liquid nitrogen and lyophilizated. All products were obtained as a white solid. The respective yields are given in Table 2.

(*E*)-5-(2-carbomethoxyvinyl)-2′-deoxyuridine (**3**)

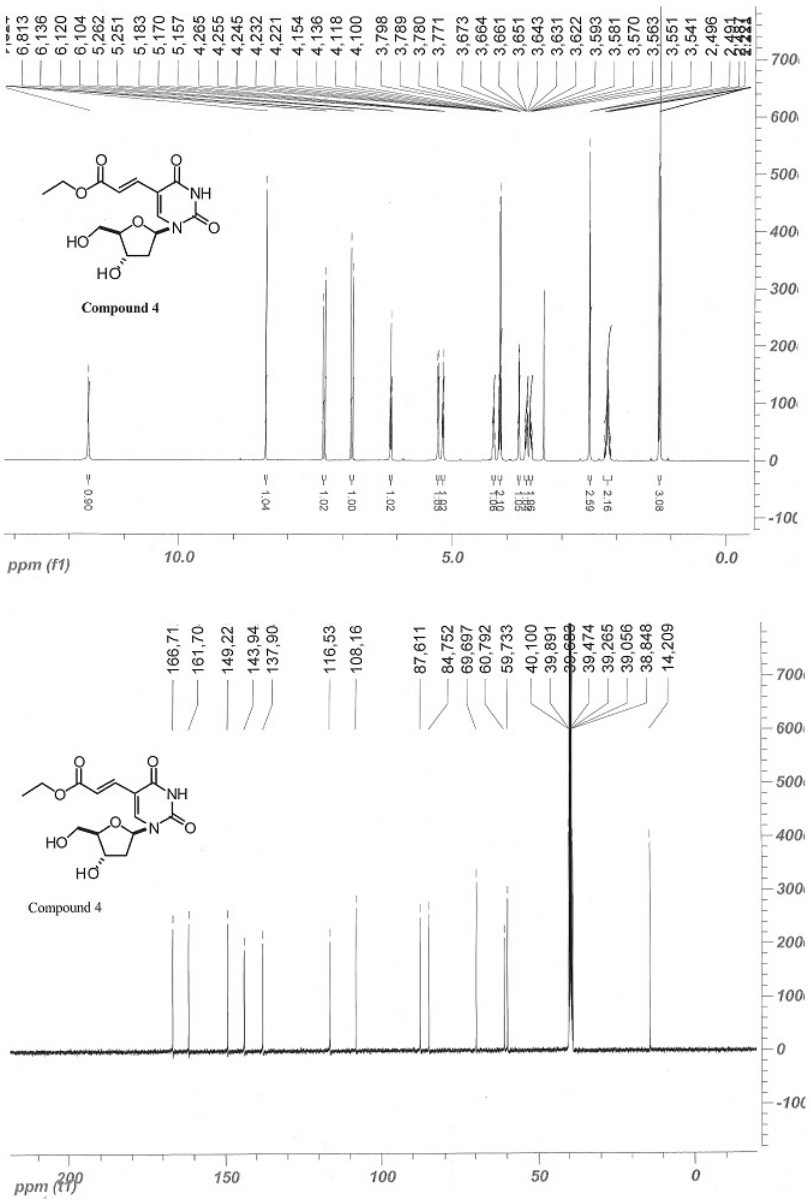


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 2.17 (m, 2H, H-2’), 3.55 (m, 1H, H-3’), 3.59 (m, 1H, H-4’), 3.66 (s, 3H, OC*H*$_3$), 3.79 (dd, , 1H, H-5’, $J_{5'a\text{-}6}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 4.24 (m, 1H, H-5’), 5.17 (t, 1H, O*H*, J = 5.6 Hz,), 5.25 (d, 1H, O*H* , J = 4.4Hz,), 6.12 (t, 1H, H-1’, $J_{1',2'a} = J_{1',2'b}$ = 6.4 Hz), 6.86 (d, 1H, H-2”, $J_{1''\text{-}2''}$ = 15.8 Hz), 7.38 (d , 1H, H-1”, $J_{1''\text{-}2''}$ = 15.8Hz), 8.41 (s, 1H, H-6), 11.65 (s, 1H, N*H*)

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ = 51.2 (*C*H$_3$), 60.7 (C-5’), 69.6 (C-3’), 84.7 (C-1’), 87.6 (C-4’), 108.1 (C-5), 116.1 (C-2”), 138.1 (C-1”), 144.0 (C-6), 149.2 (C-2), 161.6 (C-4), 167.1 (*C*OOCH$_3$). One signal (C-2’) is hidden in the solvent peaks.

MS (ESI): m/z = 335.09 [M + Na$^+$]

(*E*)-5-(2-carboethoxyvinyl)-2′-deoxyuridine (**4**)

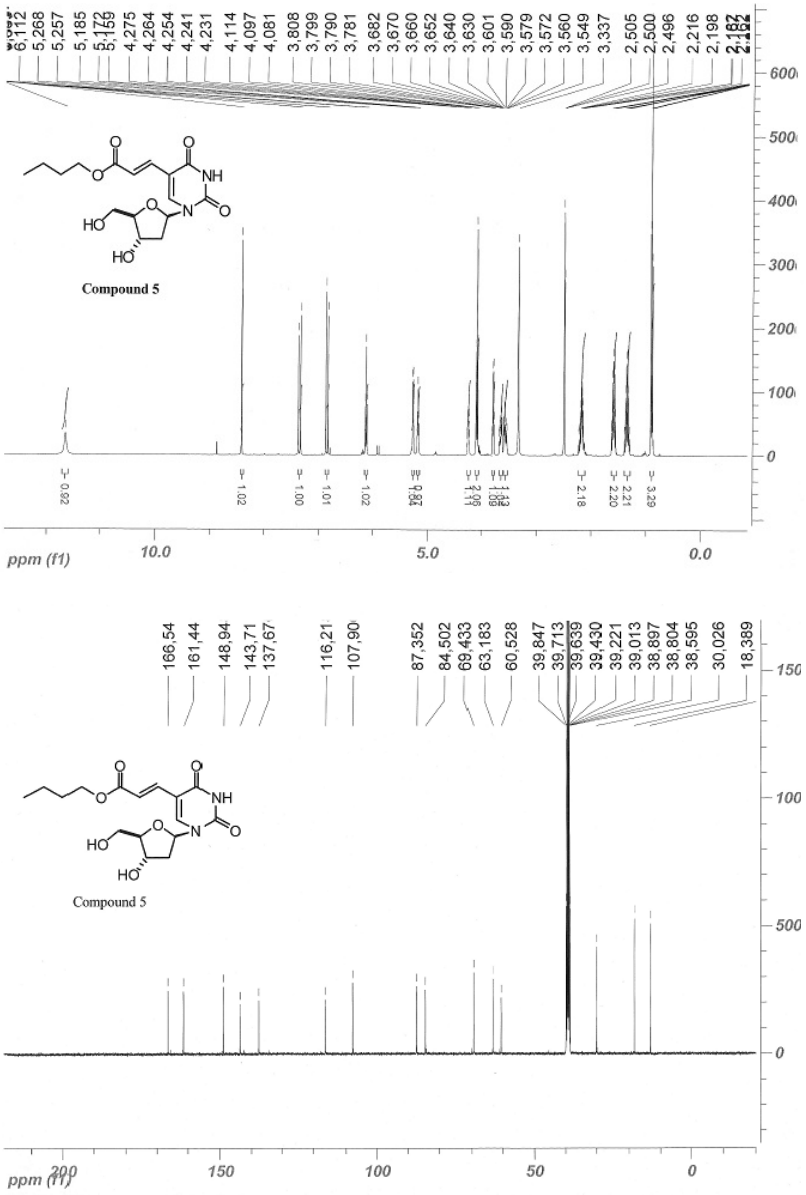


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 1.21 (t, 3H, C*H*$_3$, J = 7.0 Hz), 2.15 (m, 2H, H-2'), 3.56 (m, 1H, H-3'), 3.64 (m, 1H, H-4'), 3.78 (dd, 1H, H-5', $J_{5'a\text{-}6}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 4.11 (q, 2H, CH_2, J = 7.0 Hz), 4.23 (m, 1H, H-5'), 5.17 (t, 1H, O*H*, J = 5,2 Hz), 5.25 (d, 1H, O*H* , 4.4 Hz), 6.12 (t, 1H, H-1', $J_{1',2'a}$ = $J_{1',2'b}$ = 6.4 Hz), 6.81 (d, 1H, H-2", $J_{1"\text{-}2"}$ 15.6 Hz), 7.32 (d, 1H, H-1", $J_{1"\text{-}2"}$ = 15.6 Hz), 8.4 (s, 1H, H-6), 11.67 (s, 1H, N*H*).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =14.2 (*C*H$_3$), 59.7 (*C*H$_2$), 60.7 (C-5'), 69.6 (C-3') , 84.7 (C-1'), 87.6 (C-4'), 108.1 (C-5), 116.5 (C-2"), 137.9 (C-1"), 143.9 (C-6), 149.2 (C-2), 161.7 (C-4), 166.7 (*C*OOEt). One signal is hidden in the solvent peaks.

MS (ESI): m/z = 349.11 [M + Na^+]

(*E*)-5-(2-carbobutyloxyvinyl)-2'-deoxyuridine (**5**)

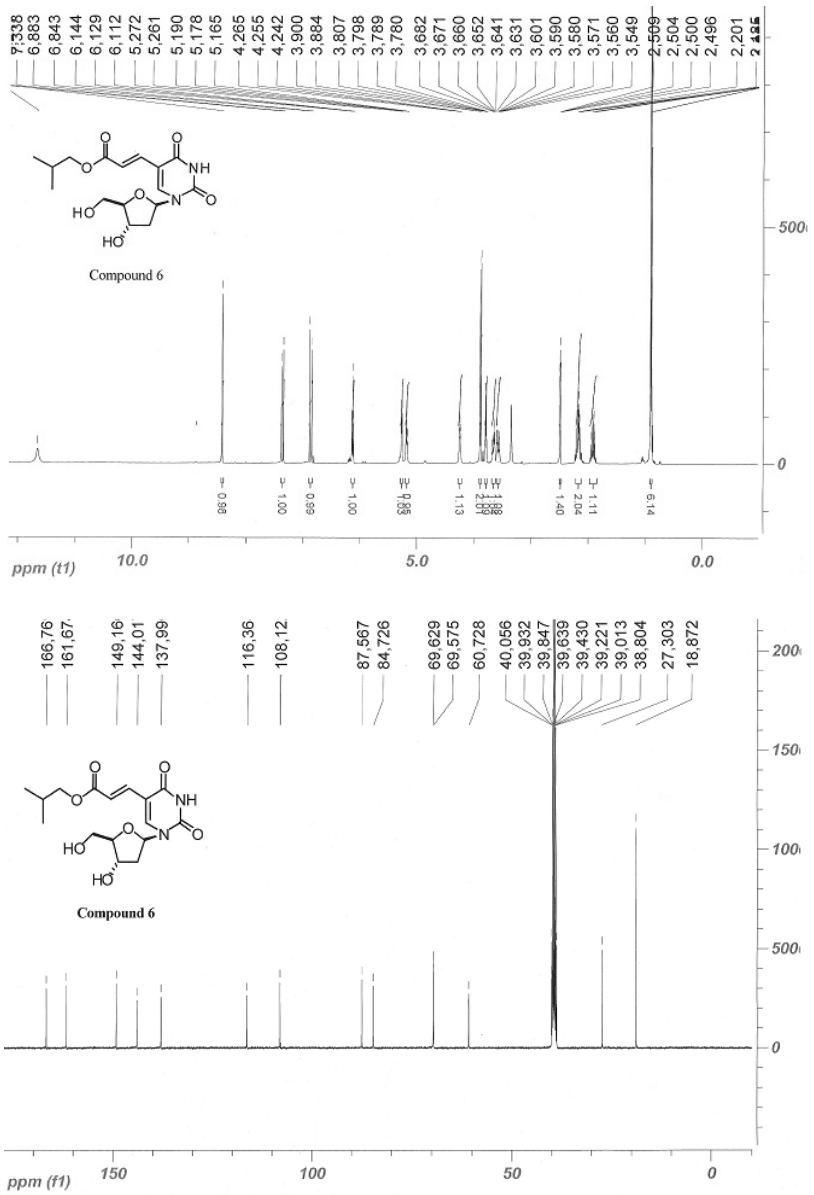


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 0.89 (t, 3H, J = 7.2 Hz, C*H*$_3$), 1.31 (2H, m, C*H*$_2$), 1.57 (2H, m, C*H*$_2$), 2.16 (2H, m, H-2'), 3.54 (2H, m,C*H*$_2$), 3.63 (1H, m, H-3'), 3.79 (dd, 1H, H-5', $J_{5'a\text{-}4'}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 4.09 (2H, t, 3.6 Hz, H-4'), 4.25 (1H, m, H-5'), 5.17 (1H, t, J =5.2 Hz, O*H*), 5.25 (1H, d, J = 4.4 Hz, O*H*), 6.12 (1H, t, H-1', $J_{1',2'a}$ = $J_{1',2'b}$ = 6.8 Hz), 6.82 (1H, d, H-2", $J_{1"\text{-}2"}$ 15.8 Hz), 7.32 (1H, d, 1H, H-1", $J_{1"\text{-}2"}$ = 15.6 Hz), 8.41 (1H, s, H-6), 11.64 (1H, s, N*H*).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =13.2 (*C*H$_3$), 18.3 (*C*H$_2$), 30.0 (*C*H$_2$), 60.5 (C-5'), 63.1 (*C*H$_2$), 69.4 (C-3'), 84.5 (C-1'), 87.3 (C-4'), 107.9 (C-5), 116.2 (C-2"), 137.6 (C-1"), 143.7 (C-6), 148.9 (C-2), 161.4 (C-4), 166.5 (*C*OOBu). One signal is hidden in the solvent peaks.

MS (ESI): m/z = 377.14 [M + Na$^+$]

(*E*)-5-(2-carbo-*i*-butyloxyvinyl)-2'-deoxyuridine (**6**)

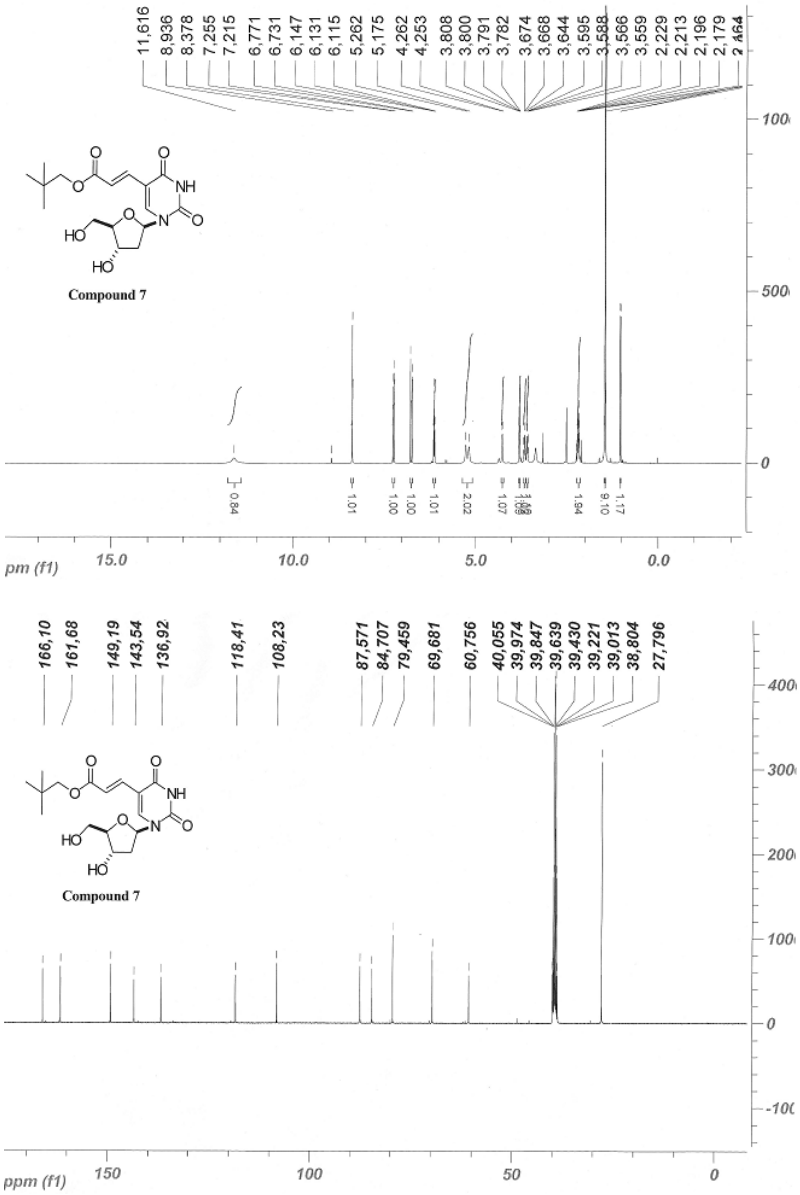


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 0.89 (d, 6H, C*H*$_3$, J = 6.4 Hz), 1.91 (m, 1H, C*H*), 2.16 (m, 2H, H-2'), 3.57 (m, 1H, H-3'), 3.65 (m, 1H, H-4'), 3.78 (dd, 1H, H-5', $J_{5'a\text{-}4}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 3.88 (d, 2H, C*H*$_2$, J = 6.4 Hz), 4.25 (m, 1H, H-5'), 5.17 (t, 1H, 5.2 Hz, O*H*), 5.26 (d, 1H, J = 4.4 Hz, O*H*), 6.12 (t, 1H, H-1', $J_{1',2'a}$ = $J_{1',2'b}$ = 6.8 Hz), 6.84 (d, 1H, H-2", $J_{1"\text{-}2"}$ 15.8 Hz), 7.33 (d, 1H, H-1", $J_{1"\text{-}2"}$= *15.8 Hz*), 8.41 (s, 1H, H-6), 11.6 (s, 1H, N*H*).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =.18.8 (*C*H$_3$), 27.3 (*C*H), 60.7 (*C*H$_2$), 69.5 (C-3'), 84.7 (C-1'), 87.5 (C-4'), 108.1 (C-5), 116.3 (C-2"), 137.9 (C-1"), 144.0 (C-6), 149.1 (C-2), 161.6 (C-4), 166.7 (*C*OOi-Bu). One signal (C-2') is hidden in the solvent peaks.

HR/MS (ESI) for $C_{16}H_{22}N_2O_7$: $[M+Na]^+$ = calcd 377.1325, found 377,1318 .

(*E*)-5-(2-carbo-*t*-butyloxyvinyl)-2'-deoxyuridine (**7**)

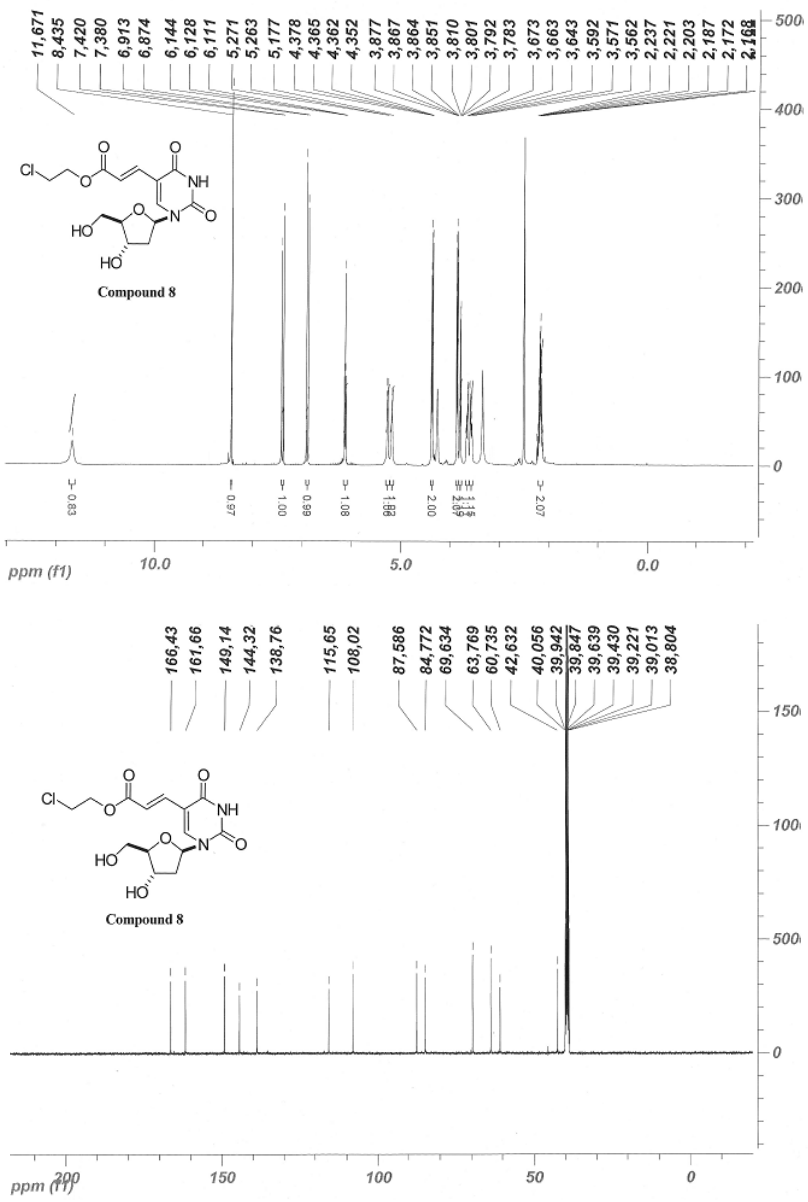


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 1.44 (s, 9H, *t*-Bu), 2.14 (m, 2H, H-2'), 3.56 (m, 1H, H-3'), 3.64 (m, 1H, H-4'), 3.79 (dd, 1H, H-5', $J_{5'a\text{-}6}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 4.25 (m, 1H, H-5'), 5.17 (bs, 1H, O*H*), 5.26 (bs, 1H, O*H*), 6.11 (t, 1H, H-1', $J_{1',2'a}$ = $J_{1',2'b}$ = 6.4 Hz), 6.73 (d, 1H, H-2", $J_{1"\text{-}2"}$ = 16 Hz), 7.21 (d, 1H, H-1", $J_{1"\text{-}2"}$ = 16 Hz), 8.37 (s, 1H, H-6), 11.61 (s, 1H, N*H*).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =, 27.9 (*t*-Bu), 60.7 (C-5'), 69.6 (C-3'), 79.4 (*C*Me3), 84.7 (C-1'), 87.5 (C-4'), 108.2 (C-5), 118.4 (C-2"), 136.9 (C-6), 143.5 (C-1"), 149.1 (C-2), 161.6 (C-4), 166.1(*C*OO*t*-Bu). One signal (C-2') is hidden in the solvent peaks.

MS (ESI): m/z = 377.13 [M + Na$^+$]

(*E*)-5-(2-carbo-2-chloroethyloxyvinyl)-2'-deoxyuridine (**8**)

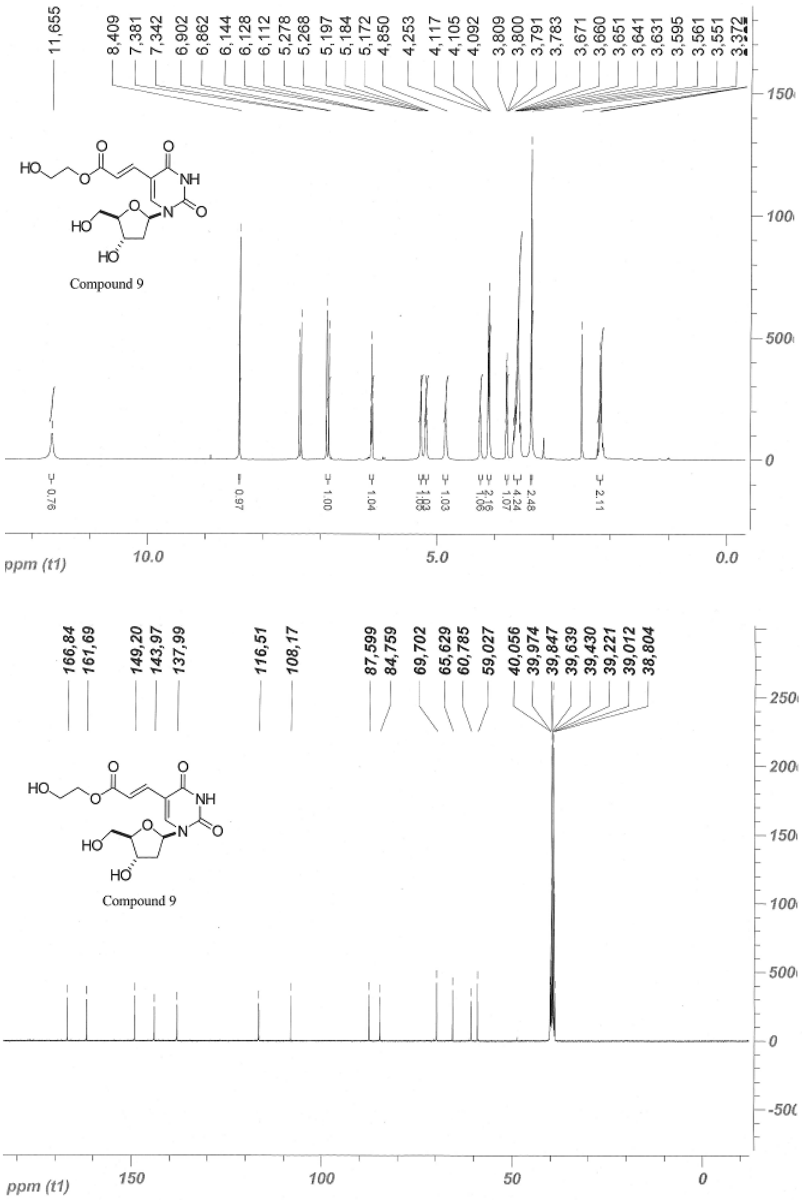


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 2.17 (m, 2H, H-2'), 3.56 (m, 1H, H-3'), 3.64 (m, 1H, H-4'), 3.79 (dd, 1H, H-5', $J_{5'a\text{-}6}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 3.86 (t, 2H, CH_2, J = 5.3 Hz), 4.36 (t, 2H, CH_2, J = 5.3 Hz), 5.17 (m, 1H, O*H*), 5.30 (m, 1H, O*H*), 6.12 (t, 1H, $J_{1',2'a}$ = $J_{1',2'b}$ = 6.8 Hz, H-1'), 6.87 (d, 1H, H-2", $J_{1"\text{-}2"}$ = 15.7 Hz), 7.38 (d, 1H, H-1", $J_{1"\text{-}2"}$ = 15.7 Hz), 8.43 (s, 1H, H-6), 11.6 (s, 1H, N*H*)

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =. 42.6 (*C*H_2), 60.7 (C-5'), 63.7 (*C*H_2) , 69.6 (C-3'), 84.7 (C-1'), 87.5 (C-4'), 108.0 (C-5), 115.6 (C-2"), 138.7 (C-1"), 144.3 (C-6), 149.1 (C-2), 161.6 (C-4), 166.4 (*C*OOEtCl). One signal (C-2') is hidden in the solvent peaks.

HR/MS (ESI) for $C_{14}H_{17}ClN_2O_7$: $[M+Na]^+$ = calcd 383.0622, found 383.0616 .

(*E*)-5-(2-carbo-2-hydroxyethyloxyvinyl)-2'-deoxyuridine (**9**)

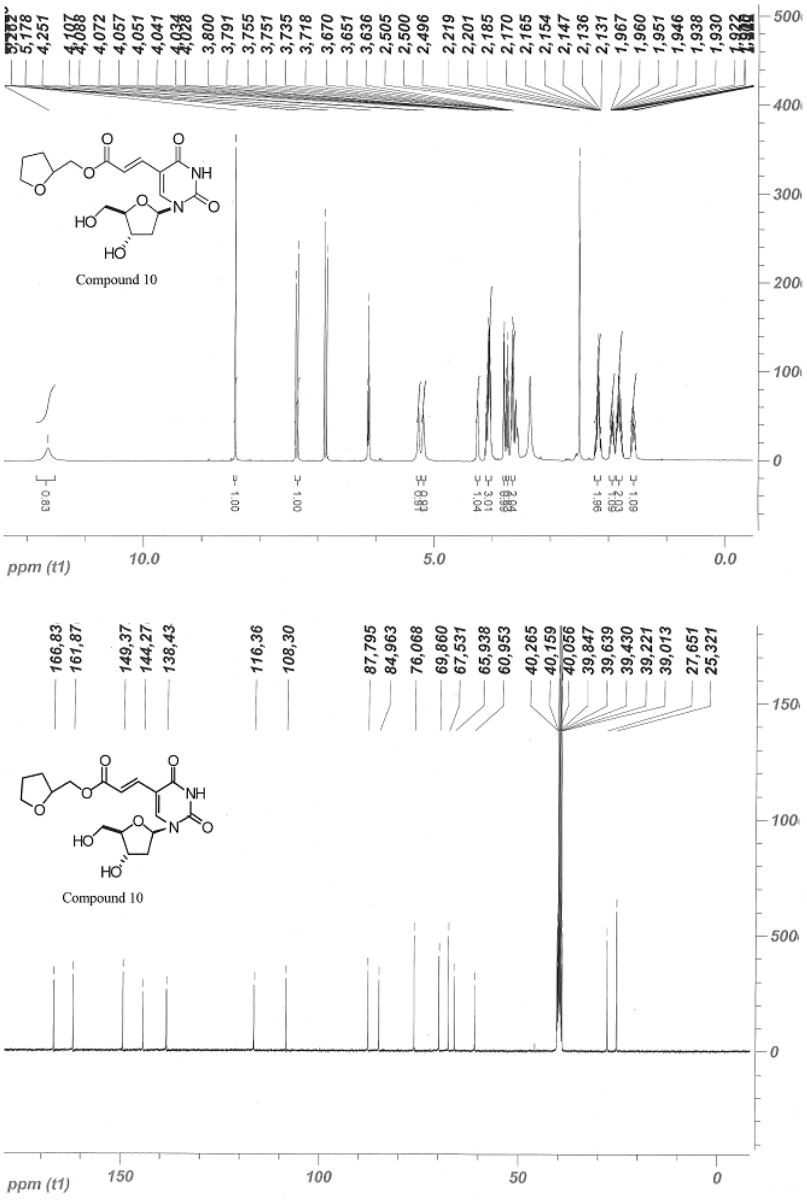


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 2.16 (m, 2H, H-2'), 3.37 (m, 2H, H-3', H-4'), 3.63 (m, 4H, C*H*$_2$), 3.79 (dd, 1H, H-5', $J_{5'a\text{-}6}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 4.25 (m, 1H, H-5'), 4.85 (m, 1H, O*H*), 5.18 (t, 1H, J = 4.8 Hz, O*H*), 5.27 (d, 1H, J = 5Hz, O*H*), 6.12 (t, 1H, H-1', $J_{1',2'a}$ = $J_{1',2'b}$ = 6.4 Hz), 6.86 (d, 1H, H-2", $J_{1"\text{-}2"}$ = 15.8 Hz), 7.34 (d, 1H, H-1", $J_{1"\text{-}2"}$ = 15.8 Hz), 8.40 (s, 1H, H-6), 11.6 (s, 1H, N*H*).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =. 59.0 (CH_2), 60.7 (C-5'), 65.6 (CH_2), 69.7 (C-3'), 84.7 (C-1'), 87.5 (C-4'), 108.1 (C-5), 116.5 (C-2"), 137.9 (C-1"), 143.9 (C-6), 149.2 (C-2), 161.6 (C-4), 166.8 (*C*OOEtOH). One signal (C-2') is hidden in the solvent peaks.

HR/MS (ESI) for $C_{14}H_{18}N_2O_8$: $[M+Na]^+$ = calcd 365.0961, found 365.0957 .

(*E*)-5-(2-carbo-2-tetrahydrofuryloxyvinyl)-2'-deoxyuridine (**10**)

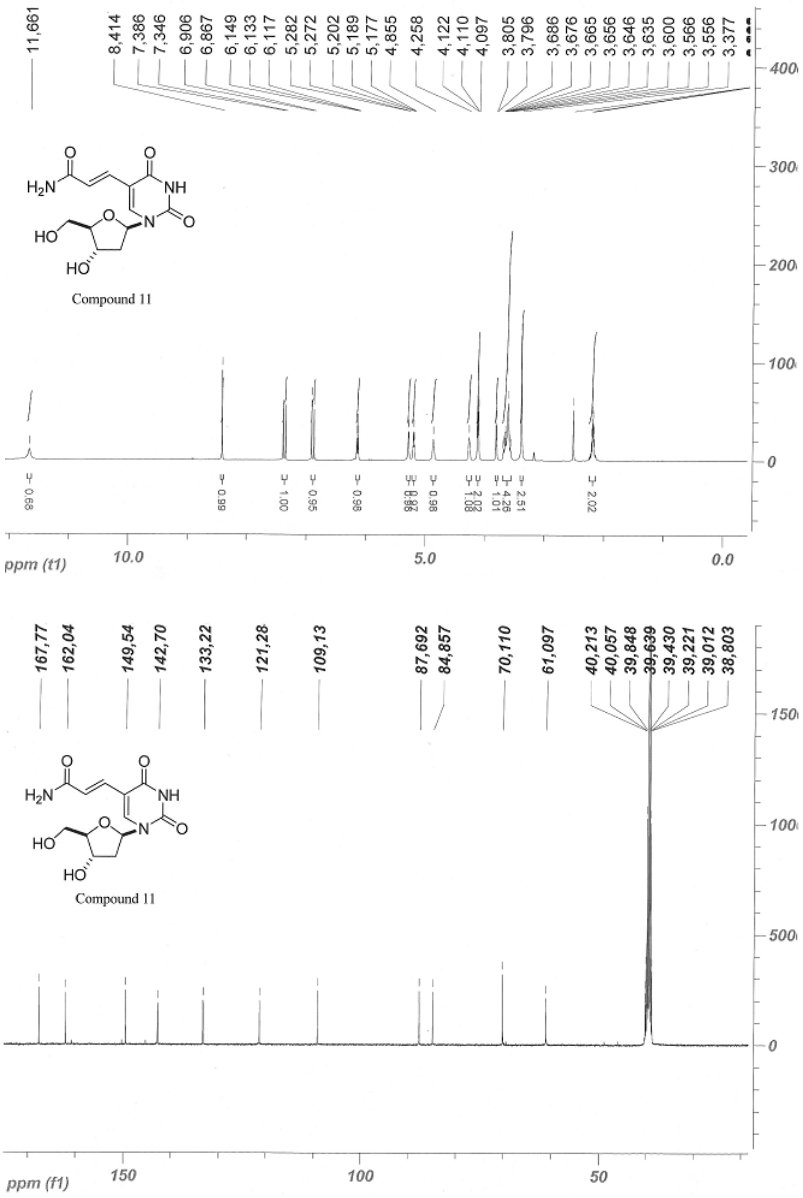


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 1.56 (m, 1H, C*H*), 1.82 (m, 2H, CH_2), 1.93 (m, 1H, C*H*), 2.15 (m, 2H, H-2'), 3.34 (m, 2H, CH_2), 3.65 (m, 2H, H-3', H-4'), 3.79 (dd, 1H, H-5', $J_{5'a\text{-}6}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 4.05 (m, 3H, CH_2, C*H*), 4.25 (m, 1H, H-5'), 5.1 (bs, 1H, O*H*), 5.2 (bs, 1H, O*H*), 6.12 (t, 1H, H-1', $J_{1',2'a} = J_{1',2'b}$ = 6.8 Hz), 6.86 (d, 1H, H-2", $J_{1"\text{-}2"}$ = 16 Hz), 7.36 (d, 1H, H-1", $J_{1"\text{-}2"}$ = 16 Hz), 8.42 (s, 1H, H-6), 11.6 (s, 1H, N*H*)

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =. 25.3 (CH_2), 27.6 (CH_2), 60.9 (C-5'), 65.9 (, 67.5, 69.8 (C-3'), 76.0, 84.9 (C-1'), 87.7 (C-4'), 108.3 (C-5), 116.3 (C-2"), 138.4 (C-1"), 144.2 (C-6), 149.3 (C-2), 161.8 (C-4), 166.8 (*C*OOCH$_2$Furfuryl). One signal (C-2') is hidden in the solvent peaks.

HR/MS (ESI) for $C_{17}H_{22}N_2O_8$: $[M+Na]^+$ = calcd 405.1274, found 405.1274 .

(*E*)-5-(2-acrylamidevinyl)-2’-deoxyuridine (**11**)

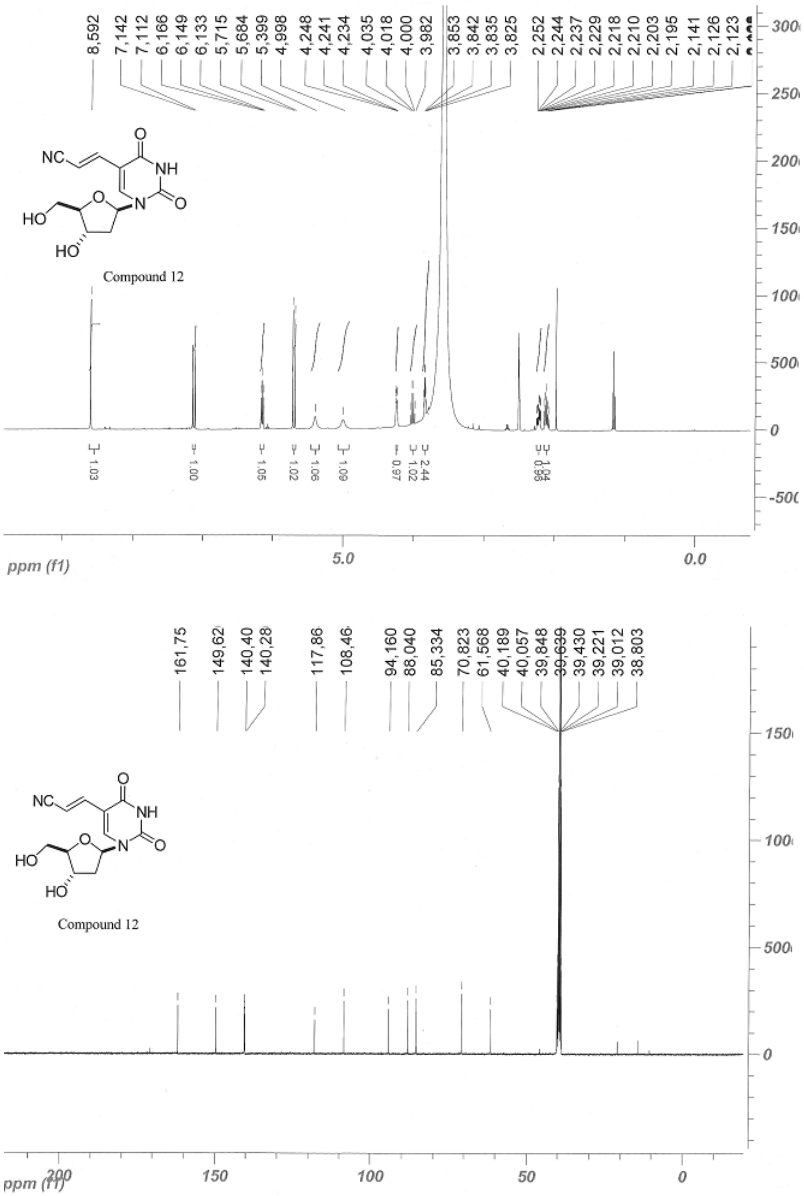


NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 2.17 (m, 2H, H-2’), 3.55 (m, 1H, H-3’), 3.59 (m, 1H, H-4’), (3.79, dd, 1H, H-5’, $J_{5'a\text{-}6}$= 3.6 Hz, $J_{5'a\text{-}5'b}$= 12 Hz), 4.11 (t, 2H, N*H*$_2$, J = 5.0 Hz,), 4.25 (m, 1H, H-5’), 5.19 (t, 1H, O*H*, J = 4.8 Hz), 5.27 (d, 1H, O*H*, J = 4 Hz), 6.13 (t,1H, H-1’, $J_{1',2'a}$ = $J_{1',2'b}$ = 6.4 Hz), 6.88 (d, 1H, H-2”, $J_{1''\text{-}2''}$ = 15.8 Hz), 7.36 (d, 1H, H-1”, $J_{1''\text{-}2''}$ = 15.8 Hz), 8.41 (s, 1H, H-6), 11.6 (s, 1H, N*H*).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =. 60.8 (C-5’), 69.8 (C-3’), 84.6 (C’1), 87.4 (C-4’), 108.9 (C-5), 121.0 (C-2”), 132.9 (C-1”), 142.4 (C-6), 149.3 (C-2), 161.8 (C-4), 167.5 (*C*OONH$_2$). One signal (C-2’) is hidden in the solvent peaks.

MS (ESI): m/z = 320.09 [M + Na$^+$]

(*E*)-5-(2-cyanovinyl)-2'-deoxyuridine (**12**)



NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 2.10 (m, 1H, H-2'), 2.21 (m, 1H, H-3'), 3.82 (dd, 1H,H-5' J = 6.8 Hz), 4.00 (m, 1H, H'4), 4.24 (m, 1H, H-5'), 4.99 (bs, 1H, O*H*), 5.39 (bs, 1H, O*H*), 5.69 (d, 1H, H-2", $J_{1"\text{-}2"}$ = 12.2 Hz), 6.14 (t, 1H, H-1', $J_{1',2'a} = J_{1',2'b} = 6.4$ Hz), 7.12 (d, 1H, H-1", $J_{1"\text{-}2"}$ = 12.2 Hz), 8.59 (s, 1H, H-6).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =. 61.3 (C-5'), 70.6 (C-3'), 85.1 (C-1'), 88.0 (C-4'), 93.9 (CN), 108.2 (C-5), 117.6 (C-2"), 140.0 (C-1"), 140.2 (C-6), 149.4 (C-2), 161.5 (C-4). One signal (C-2') is hidden in the solvent peaks.

MS (ESI): m/z = 302.08 [M + Na^+]

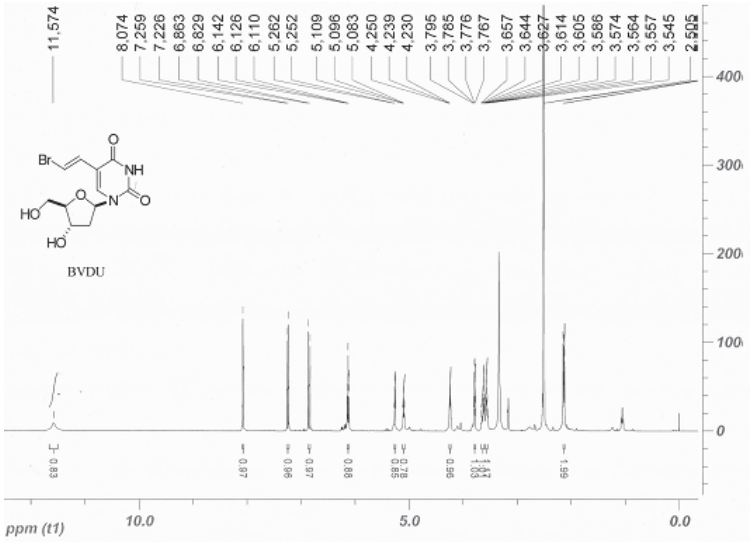
Procedure for the totally aqueous ligand-free synthesis of BVDU.

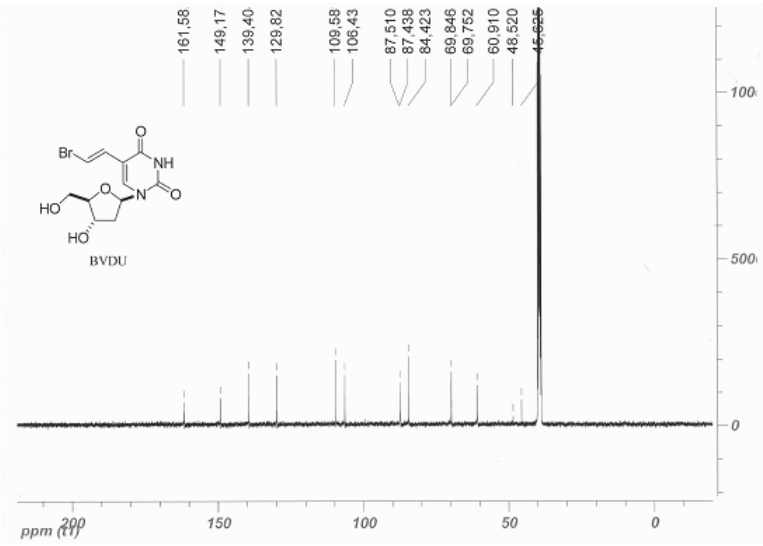
A - Obtention of (E)-5-(2-carboxyvinyl)-2'-deoxyuridine (CVU)

A solution of compound **3** (obtained as described just before) (100mg, 0.320 mmol) in aqueous sodium hydroxyde (1M, 5 mL) was stirred overnight at room temperature. The solution was then cooled to 0°C and brought to pH 2 by addition of HCl 4M. The mixture was left to stand in ice and the white precipitate was filtered. The filtrate was evaporated to dryness under reduce pressure. Water (2 mL) was added and the resulting precipitate was filtered. The combined precipitates were lyophilizated to give the desired CVU as a white solid (86 mg, 90 %).

B - Obtention of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)

To a solution of CVU (85 mg, 0.28 mmol) in freshly degazed water (5 mL) was added acetate potassium (54.86 mg, 0.56 mmol). The solution was heated (60 °C). While still hot, NBS (49.8 mg, 0.28 mmol) was added in small portions. The mixture was then cooled to room temperature for 2 hours. The mixture was evaporated to dryness under reduce pressure and the residue was purified by flash-chromatography on C18 silica (H_2O:MeOH 95:5 to 5:95). The fractions were combined and methanol was removed under reduce pressure. The remaining solution was frozen with liquid nitrogen and lyophilizated. BVDU was obtained in 69% yield as a white powder.





NMR ^{1}H (400 MHz, DMSO-*d*$_6$) δ = 2.12 (m, 2H, H-2'), 3.54 (m, 1H, H-2'), 3.60 (m, 1H, H-4'), 3.77 (dd, 1H,H-5' J = 6.8 Hz), 4.20 (m, 1H, H'5), 5.09 (t, 1H, O*H, J* = 5.2 Hz), 5.39 (d, 1H, O*H*, J = 4 Hz), 5.69, 6.12 (t, 1H, H-1', $J_{1',2'a} = J_{1',2'b}$ = 6.4 Hz), 6.84(d, 1H, H-2", $J_{1"-2"}$ = 13.4 Hz), 7.23 (d, 1H, H-1", $J_{1"-2"}$ = 12.2 Hz), 8.07 (s, 1H, H-6), 11.5 (s, 1H, N*H*).

NMR^{13}C (101 MHz, DMSO-*d*$_6$) δ =. 45.6 (C-2'), 60.9 (C-5'), 69.7 (C-3'), 84.4 (C-1), 87.5 (C-4'), 106.4 (C-5), 109.5 (C-2"), 129.8 (C-1"), 139.4 (C-6), 149.4 (C-2), 161.5 (C-4).

MS (ESI): m/z = 377.99 [M + Na^+]